objected to by the Examiner from claims 43-51 and canceling claims 52-58. Accordingly, entry of the above amendments will, at a minimum, reduce the issues for appeal by obviating the Section 112, second paragraph, rejection of claims 43-58. Entry of the above amendments is requested.

It is the undersigned's understanding that the Examiner was concerned about the claim recitation to metastatic tumors generally as the Examiner was understood to believe that only metastatic melonoma had been exemplified. Attached are copies of patient studies which demonstrate that a variety of metastatic tumor types are treatable. The patient studies show that tumors, such as squamous carcinmoa, lung carcinoma, large bowel carcinoma, ovarian tumors and renal cell carcinoma, as well as melanoma, are treatable. Specifically, the attached "Neuropathology" reports indicate the origin of the tumors tested. The names and other patient information, as well as the dates of the reports, have been removed from the attached. These Neuropathology reports were produced after the filing of the priority application. The attached Neuropathology reports have been edited to include a patient one letter, or letter-number, code in the "Surname" indication which corresponds with the samples of the attached Figures 1-10, wherein virus growth of 17+ (non-deleted virus control) and 1716 (exemplification of the presently claimed invention) is demonstrated. These patient studies are submitted to demonstrate that mutant virus 1716 (as an example of the presently claimed invention) is capable of replicating (i.e., growing) in metastatic tumour cells present in the brain.

Specifically, each patient was treated with the virus and, at various time points, cells were removed and tested for the presence of the virus. The results show that

1716 was capable of replicating in the tumour cells, and thus provides an effective tool for selectively lysing cancer cells.

Each virus growth graph shows the growth of HSV-1 strain 17 (17+) and HSV-1 strain 17 mutant 1716 (1716) in either Baby Hamster Kidney cells or 3T6 cells. BHK cells are used to grow the virus. These cells represent tumour cells as they are continuously dividing cells. They are a transformed cell line in which cells continuously divide and do not differentiate. 3T6 cells are mouse embryo fibroblasts which are growth inhibited on contact. Therefore, these cells represent normal (non-neoplastic) cells. Each graph shows that 1716 is capable of replicating in the patient's tumour cells, whatever the primary origin of the tumour.

Attached is a Declaration by the undersigned submitted in response to the Examiner's comment in paragraph 3 of page 2 of the Office Action dated April 5, 2001 (Paper No. 25). Entry of the amendment to the specification of January 22, 2001, is requested. The undersigned notes that the entirety of the referenced document, i.e., WO 92/13943, was incorporated by reference and the attached Declaration indicates the cited U.S. patent, is, in substance, the same as the originally referenced document. The applicants note that strain 1716 was deposited and assigned Accession No. V92012803, as is clear from pages 26 and 27 of WO 92/13943 and columns 12, 15 and 16 of U.S. Patent No. 6,040,169. Pages 26 and 28 of WO 92/13943 further indicates that strain 1714 has also been deposited under conditions of the Budapest Treaty and has been assigned the Accession No. V92012802. See, also, columns 12-14 of U.S. Patent No. 6,040,169. Accordingly, one of ordinary skill in the art would appreciate that

page 26 of WO 92/13943 does not state that strains 1716 have been deposited with two different Accession Numbers as stated by the Examiner on page 2 of Paper No. 25. The Examiner is requested to contact the undersigned however if any further clarification is required.

The Section 112, first paragraph, rejection of claims 43-50 and 52-57 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner continues to believe that the "mutations as claimed are unlimited and can be made in any portion HSV-1 and the effects of these mutations on virus function are not predictable." See, page 3 of Paper No. 25. The Examiner goes on to state that the specification only describes, in her view, a very specific mutation within γ35.5 in a long repeat of HSV-1. The applicants again submit in response that the subject matter of claim 43 (and claim 52) do not relate to a "whole universe of HSV-1 mutants" but rather require a very specific class of mutants which are defined as having a non-functional γ34.5 gene in the long repeat region R_L. The recited gene does not express the normal product as a functional product of the gene. Accordingly, the claim recites a very specific mutation within the γ34.5, such as in the long repeat region of HSV-1 (claim 46), as referred to by the Examiner as being described in the specification. The Examiner is urged to appreciate that the recited HSV is a mutant because it has a non-functional γ34.5 gene. The applicants submit that the Examiner has admitted that the specification describes "very specific mutations within γ34.5 in a long repeat region of HSV-1" while insisting that the scope of the claims covers

"mutants which are unlimited and can be made in any portion of the HSV-1". The applicants respectfully submit the Examiner's comments are inconsistent and clarification is requested in the event the rejection is maintained and/or the above amendments are not entered.

Withdrawal of the Section 112, first paragraph, rejection of claims 43-50 and 52-57 is requested.

The Section 112, first paragraph, rejection of claims 51 and 58 is obviated by the attached Declaration of deposited materials. Consideration of the attached and withdrawal of the Section 112, first paragraph, rejection of claims 51 and 58 are requested.

The Section 103 rejection of claims 43-58 over U.S. Patent No. 5,585,096 in view of Olofsson (Arch. Virol., 1993, 128:241-256), Davey (Neurosurgery, 1991, 28:8-14), WO 92/13943 and Markert (Neurosurgery, 1993, 32:597-603) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments as well as the attached Declaration of Professor Cruickshank.

The applicants submit that a person working in the neuroscience field in 1994 would not have concluded from the details provided in U.S. 5,585,096 that extracranial human melanoma were treatable by use of HSV which contains a deficiency in the γ34.5 and ribonucleotide reductase genes.

It is not disputed that the production of an avirulent strain of HSV having a modification such as a deletion in the γ34.5 gene was possible in 1994. However, the

application of an avirulent HSV strain to the treatment of neoplastic cells was less well documented.

The applicants believe that it has been known for a considerable time that HSV inhibits cells of the nervous system. Thus, it may have been considered reasonable that avirulent strains of HSV could have been used to inhabit diseased cells following the replication of the virus.

U.S. 5,585,096 provides experimental evidence supporting the view that these avirulent HSV strains can be used to treat abnormal neuronal cells. In fact the patent illustrates the use of a replication competent HSV vector with defective expression of the γ34.5 and the ribonucleotide reductase gene in the treatment of primary brain tumours. The patent exemplifies the use of an avirulent strain of HSV on human brain tumours and human glioma.

The results provided in U.S. 5,585,096 show that the avirulent strain of HSV was effective at killing tumours of neuronal origin however. There is no data provided and no supporting evidence that the avirulent HSV strain could have been used in the same way to kill tumour cells of a non-neuronal origin, in a manner which is presently claimed.

The secondary references fail to cure the deficiencies of U.S. Patent No. 5,585,096, in this regard.

In view of the above and attached, the claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

B. J. Sadoff
Reg. No. **36,663**

BJS:eaw
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

MARKED UP CLAIMS

43. (Twice Amended) A method of treating a metastatic tumour which occurs in but does not originate from the central nervous system of a human which method comprises the step of administering to the said human an effective amount of an avirulent [a mutant] herpes simplex virus type 1 [which has] having a non-functional γ34.5 gene [in the long repeat region R_L, said gene having been modified by deletion, insertion or substitution such that it does not express the normal product or a functionally equivalent product of said gene and], wherein the [mutant HSV-1] herpes simple virus type 1 infects and replicates within the tumour cells of the tumour.

✓

NEUROPATHOLOGY

Lab.No.:

Surname: S
Forename:
Date of Birth:
Sex:
Reg. Number:
NHS Number:

Consultant:
Hospital: **Queen Elizabeth Hospital, B'ham**
Ward: **NCCU (Neuro Critical Care)**
Department: **Neurosurgery**
Ext. Reference:
Date Received:

Nature of Specimen: RIGHT PARIETAL LESION

Macro:

A. Tumour - Irregular pieces of haemorrhagic material, together about 2cm across.
B. Blood clot - Piece of blood clot 2 x 2 x 0.7cm.

Micro:

A. Sections show partly necrotic and haemorrhagic malignant tumour composed of diffuse sheets of large polygonal cells with round to oval, sometimes irregular, nucleus, granular chromatin, single nucleolus and moderate amounts of cytoplasm. Scattered mitoses are seen. There are no distinguishing architectural features. Immunostains for epithelial, germ cell and lymphoma markers are negative, but S-100 protein and the melanoma markers HMB-45 and Melan-A are positive. The appearance is that of metastatic malignant melanoma.

B. Blood clot only.

Conclusion: Malignant melanoma.

TX2302 M8720/6

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See Fig. 1a

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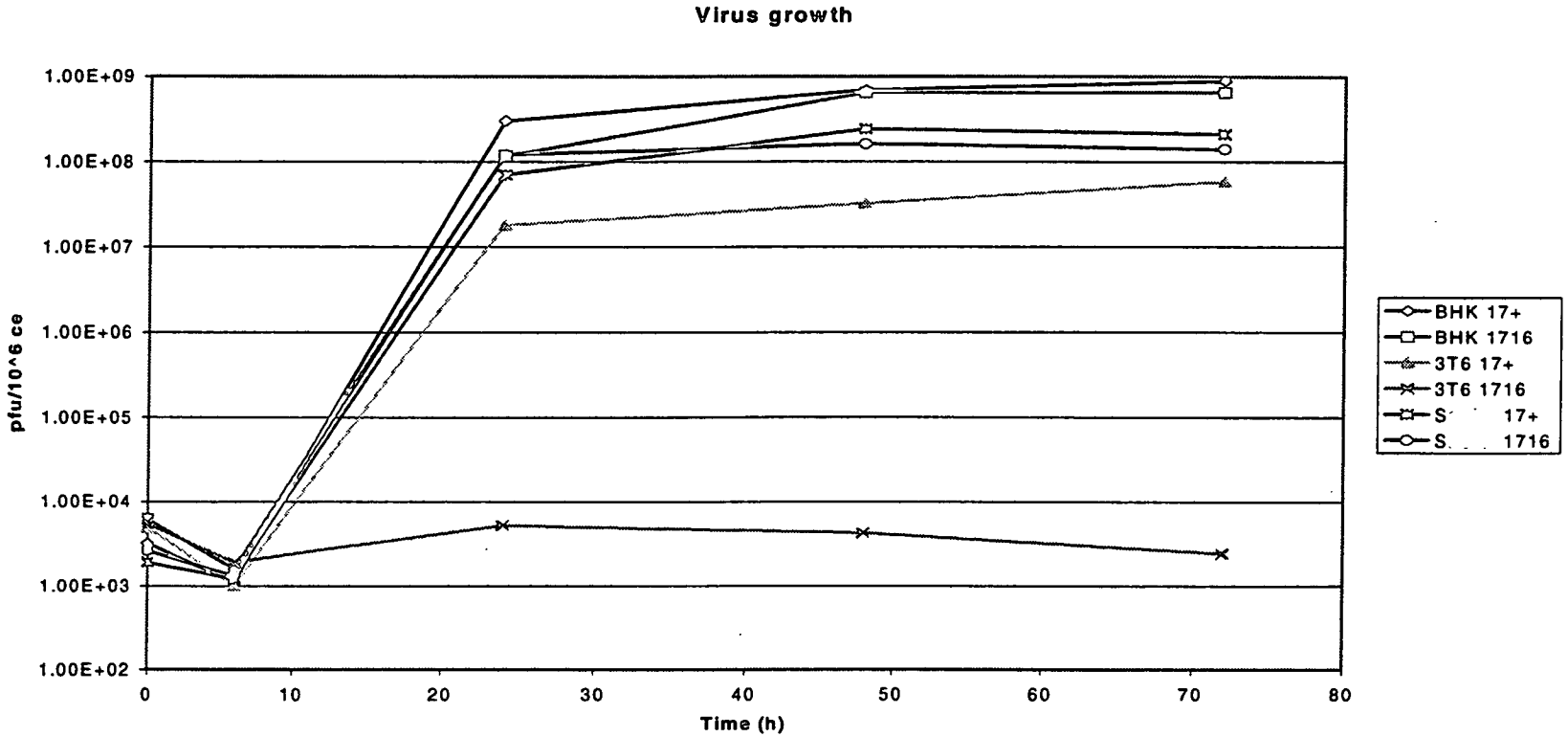
Figure 1a


Virus growth
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1.00E+08
1.00E+07
1.00E+06
1.00E+05
1.00E+04
1.00E+03
1.00E+02
pfu/10^6 ce
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80
Time (h)
BHK 17+
BHK 1716
3T6 17+
3T6 1716
S 17+
S 1716

Surname: R
Forename:
Date of Birth:
Sex:
Reg. Number:
NHS Number:

Consultant:
Hospital: Queen Elizabeth Hospital, B'ham
Ward: Ward East Lower B (Neurosurg)
Department: Neurosurgery
Ext. Reference:
Date Received:

NEUROPATHOLOGY

Nature of Specimen: RIGHT FRONTAL LESION

Macro:

Red nodule with white foci 2.5 x 2 x 1.5cm.

Micro:

Section shows a melanotic melanoma with haemorrhage and necrosis, consistent with a metastasis.

TX2202 M8720/6

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see Fig. 1b

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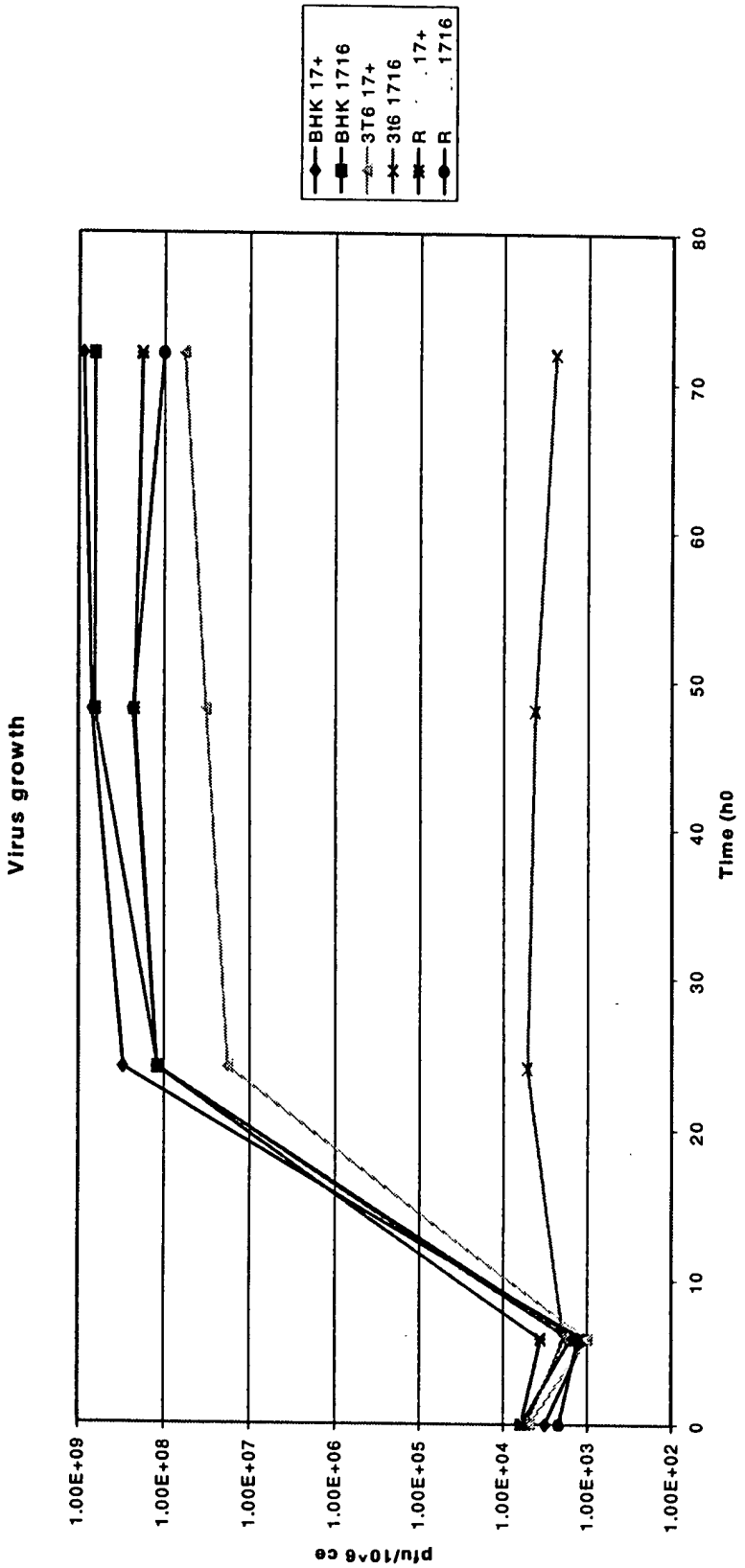
University Hospital Birmingham NHS trust

FIGURE 1b


Virus growth
BHK 17+
BHK 1716
3T6 17+
3t6 1716
R 17+
R 1716
pfu/10^6 ce
1.00E+09
1.00E+08
1.00E+07
1.00E+06
1.00E+05
1.00E+04
1.00E+03
1.00E+02
0
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Time (h0

NEUROPATHOLOGY DEPARTMENT

Lab.No.:

Surname:	F	Consultant:	
Forename:		Hospital:	Queen Elizabeth Hospital, B'ham
Date of Birth:		Ward:	Ward East Lower B (Neurosurg)
Sex:		Department:	Neurosurgery
Reg. Number:		EXT. Reference:	
NHS Number:		Date Received:	

Nature of Specimen: RIGHT FRONTAL LESION

Macro:

A: Nodule of reddish brown tissue 2 x 1.5 x 1.3cm with cystic cut surface.
B: Similar tissue to specimen A, similar dimensions.

Micro:

A&B: Extensively haemorrhagic and necrotic malignant tumour composed of sheets of large polygonal cells with round to oval nucleus containing a single large nucleolus and vaguely basophilic cytoplasm. There are scattered mitoses. Immunostains for S-100 protein and for the melanoma markers HMB-45 and Melan-A are positive. Stains for cytokeratin EMA and GFAP are negative. The appearance is that of metastatic malignant melanoma.

Conclusion: Metastatic malignant melanoma.

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See Fig. 2

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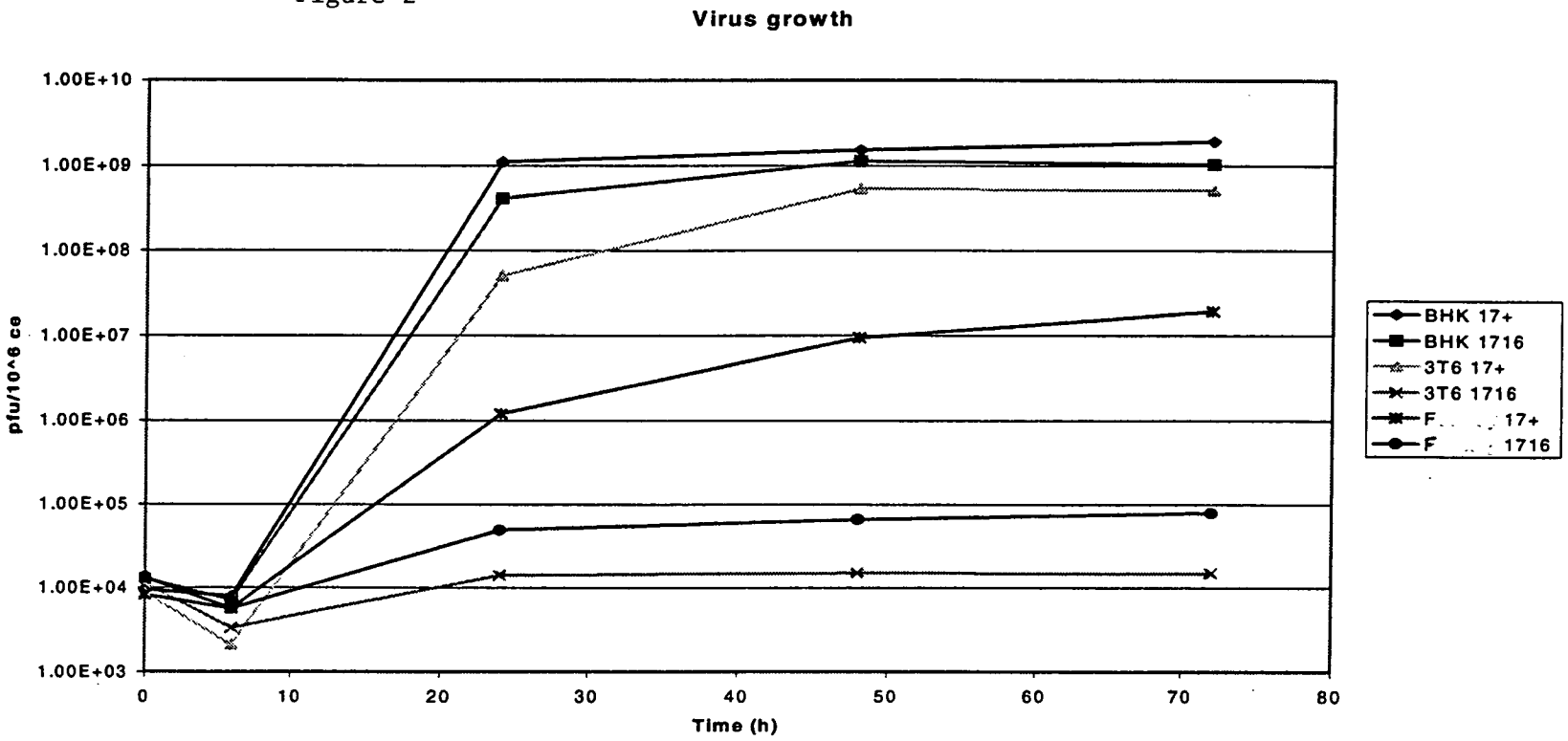
Figure 2


Virus growth
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1.00E+09
1.00E+08
1.00E+07
1.00E+06
1.00E+05
1.00E+04
1.00E+03
pfu/10^6 ce
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80
Time (h)
BHK 17+
BHK 1716
3T6 17+
3T6 1716
F 17+
F 1716

[redacted] NEUROPATHOLOGY

Lab.No.:

Surname: B
Forename:
Date of Birth:
Sex:
Reg. Number:
NHS Number:

Consultant:
Hospital: Queen Elizabeth Hospital, B'ham
Ward: Ward East Lower B (Neurosurg)
Department: Neurosurgery
Ext. Reference:
Date Received:

Nature of Specimen: POSTERIOR FOSSA LESION

Macro:

Fragments of soft, friable tissue together about 2cm across.

Micro:

Sections show partly necrotic, poorly differentiated metastatic carcinoma composed of sheets of large polygonal cells with no obvious architectural pattern. In places the tumour cell nuclei are very large and bizarrely shaped and there are multinucleate tumour giant cells. Site of origin cannot be determined, but lung would be a likely possibility.

Conclusion:

Metastatic carcinoma.

TX6000 M8010/6

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See Fig. 3

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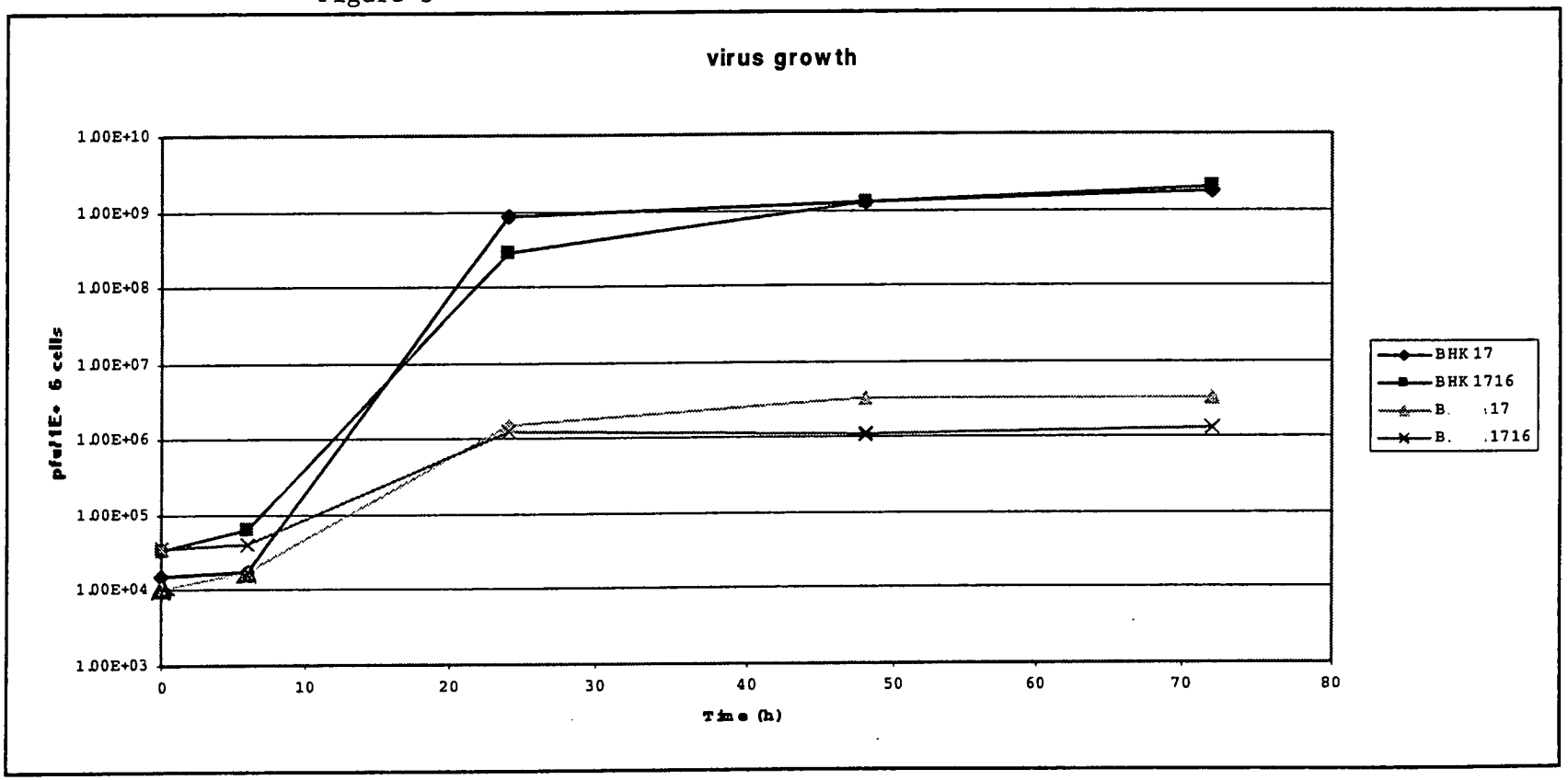
Figure 3


virus growth
1.00E+10
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1.00E+08
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1.00E+03
pfu/1E+6 cells
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Time (h)
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B. .1716

[redacted] DEPARTMENT

Lab.No:

Surname: S1
Forename:
Date of Birth:
Sex:
Reg. Number:
NHS Number:

Consultant:
Hospital: Queen Elizabeth Hospital, B'ham
Ward: NCCU (Neuro Critical Care)
Department: Neurosurgery
Ext. Reference:
Date Received:

NEUROPATHOLOGY

Nature of Specimen: LEFT FRONTAL LESION

Macro:

A) "Residual tumour ?" - irregular grey white tissue 1.3cm across.
B) "Normal tissue tumour" - grey and white tissue 1.6cm across.
C) Irregular cerebral tissue 2cm across.

Macro:

A, B and C show cerebral tissue bearing a fairly cellular astrocytic tumour with small, anaplastic nuclei, mitotic activity, several figures of serpiginous necrosis and florid microvascular (vascular endothelial) hyperplasia.

As it was removed in several pieces it is difficult to comment on completeness of excision.

Diagnosis:

Glioblastoma (astrocytoma grade 4).

TX2203 M940/3

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See Fig. 4

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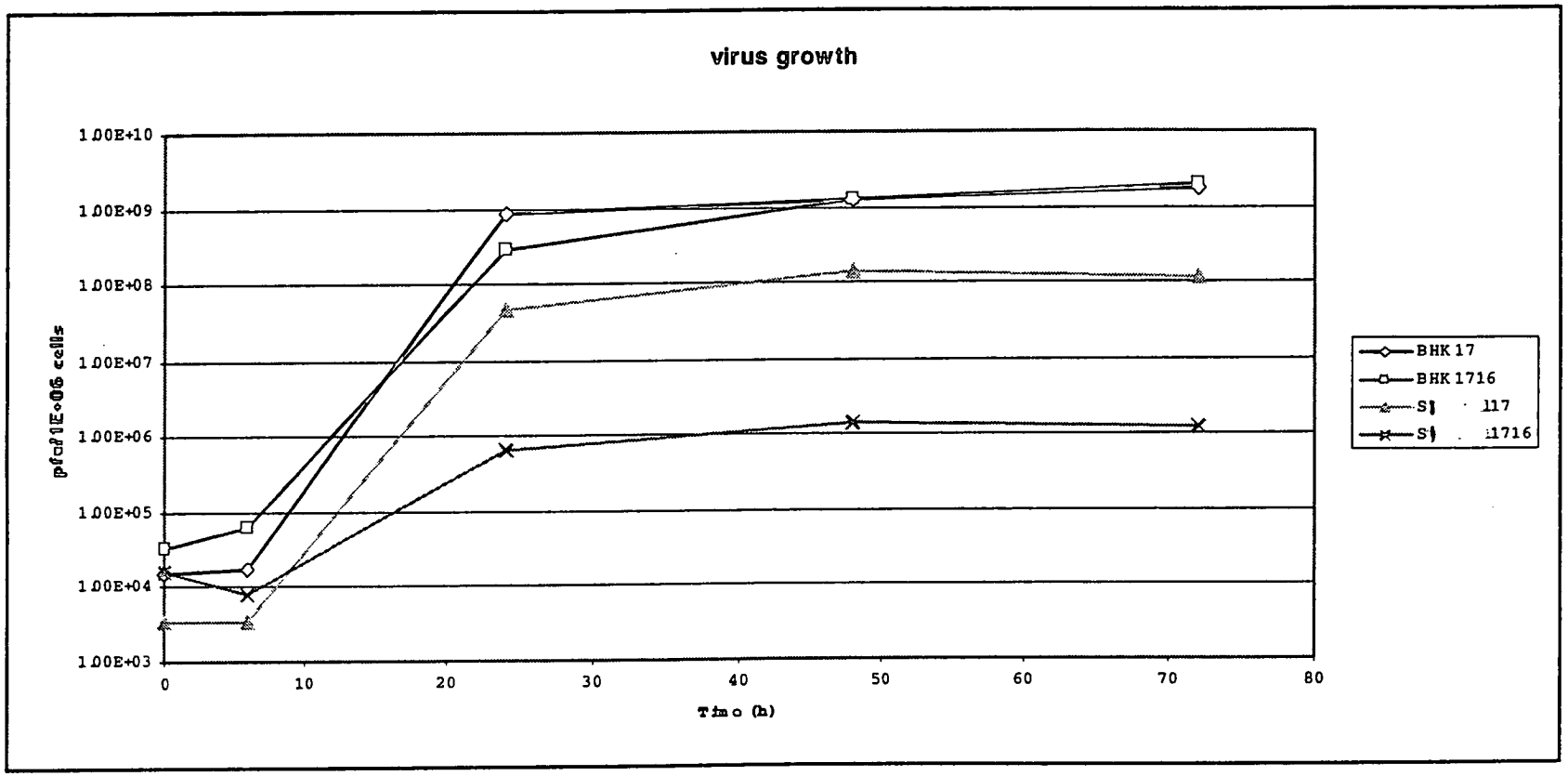
Figure 4


virus growth
1.00E+10
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BHK 17
BHK 1716

NEUROPATHOLOGY DEPARTMENT

Lab.No

Surname: K
Forename:
Date of Birth:
Sex:
Reg. Number:
NHS Number:

Consultant:
Hospital: Queen Elizabeth Hospital, B'ham
Ward: Ward East L wer A (Neurosurg)
Department: Neurosurgery
Ext. Reference:
Date Received:

Nature of Specimen: POSTERIOR FOSSA LESION

Macro:

Irregular piece of firm grey tissue 2.5 x 1.5 x 1cm, with 2 separate small fragments.

Micro:

Sections show extensively necrotic metastatic poorly differentiated carcinoma, entirely consistent with lung primary origin. Other origins cannot be excluded.

Comment: I am unsure of the exact histological type of carcinoma here. Squamous seems more likely than adenocarcinoma. In any event this is not small cell carcinoma.

Conclusion: Metastatic carcinoma.

TX6000 M8140/6

Reported by: **Date:**

see Fig. 5

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NEUROPATHOLOGY

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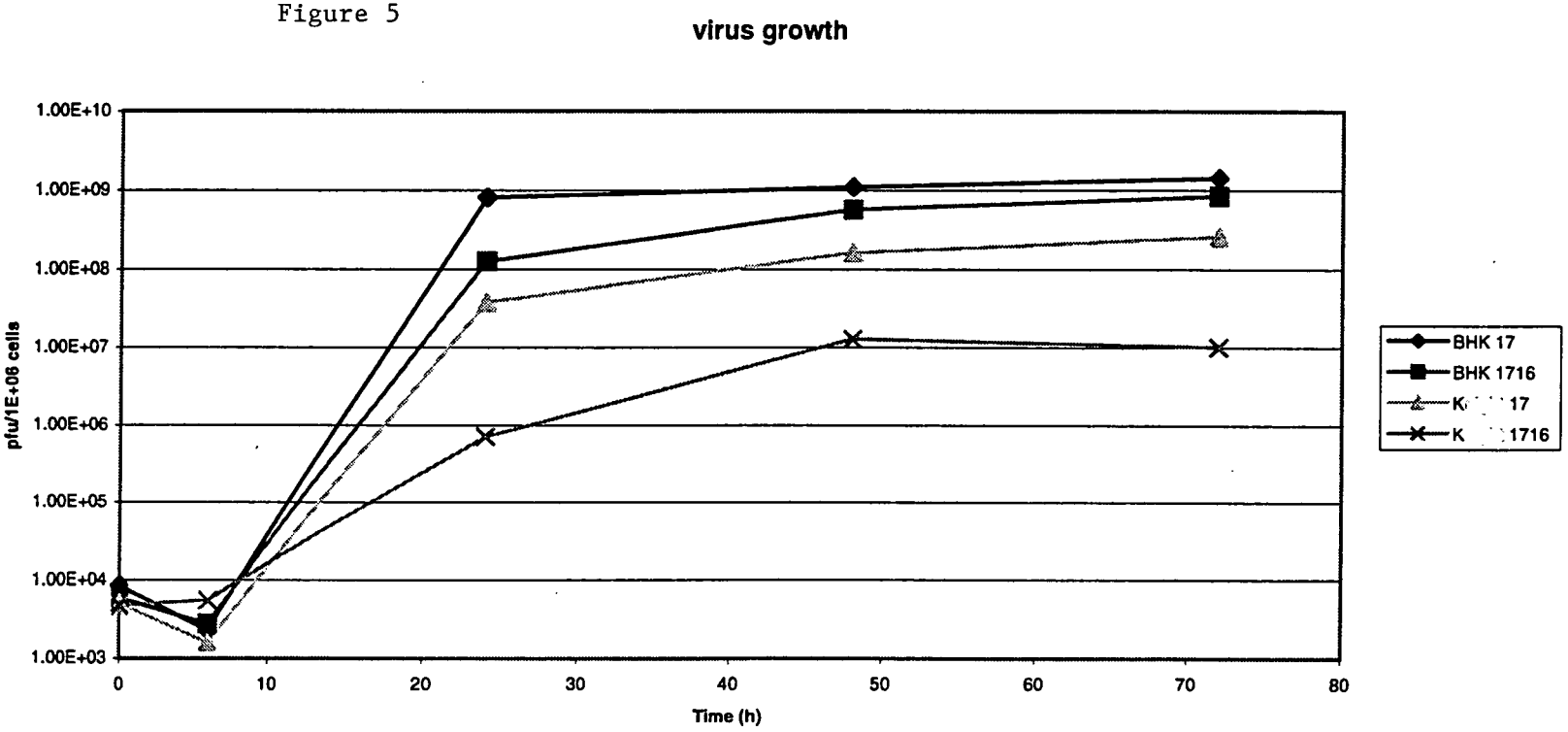
Figure 5


virus growth
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NEUROPATHOLOGY DEPARTMENT

Lab.No.:

Surname:
Forename:
Date of Birth:
Sex:
Reg. Number:
NHS Number:

Consultant:
Hospital: **Queen Elizabeth Hospital, B'ham**
Ward: **Ward East Lower B (Neurosurg)**
Department: **Neurosurgery**
Ext. Reference:
Date Received:

NEUROPATHOLOGY

Nature of Specimen: OCCIPITAL LOBE TUMOUR

Macro:

Fragments of pale and brown soft tissue together about 1.8cm.

Micro:

Sections show poorly differentiated metastatic adenocarcinoma. Lung would be one possible primary origin, but other origins should also be considered.

TX2400 M8140/6

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See Fig. 6

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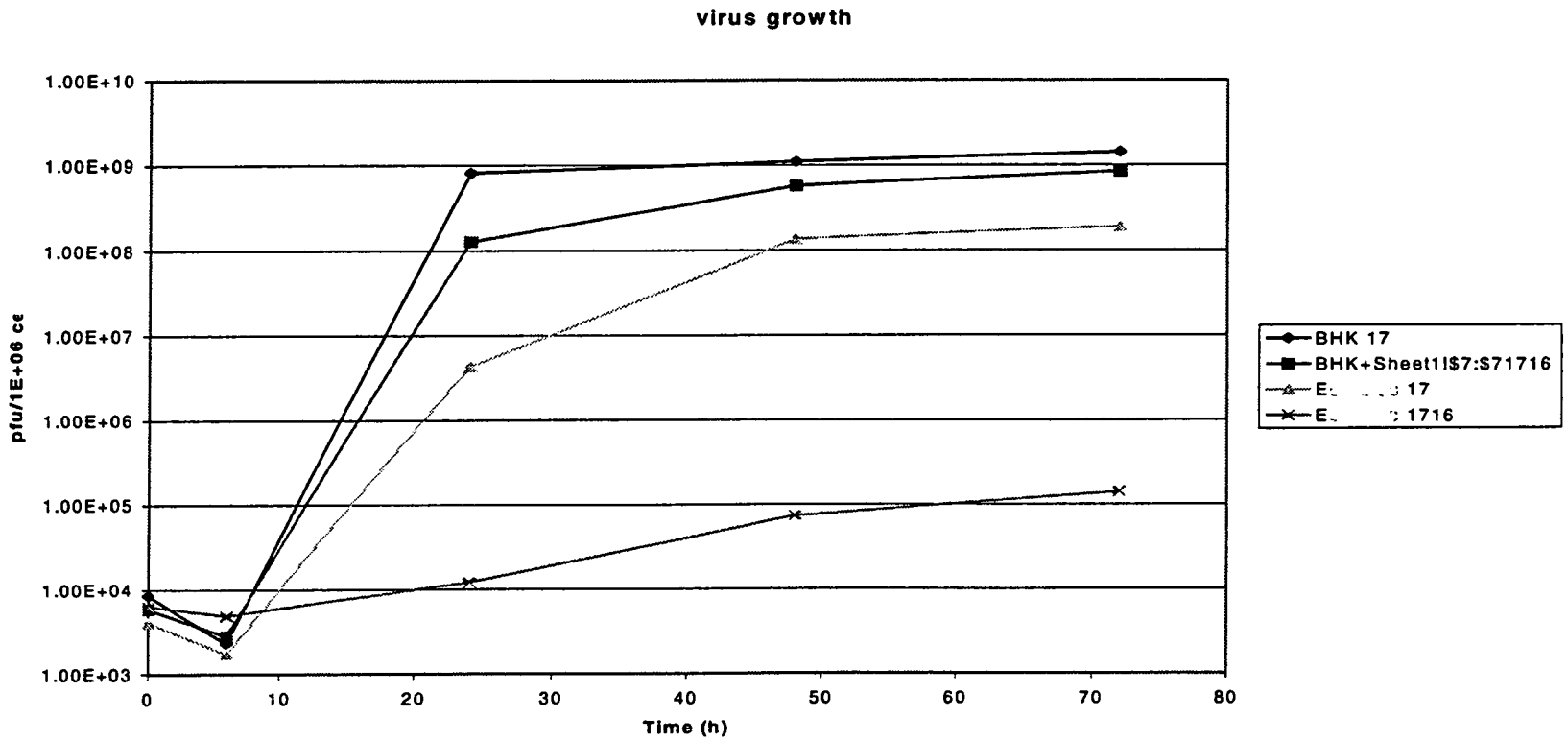
Figure 6


virus growth
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[redacted] Lab.No.:

Surname:		Consultant:	
Forename:		Hospital:	Queen Elizabeth Hospital, B'ham
Date of Birth:		Ward:	Ward East Lower B (Neurosurg)
Sex:		Department:	Neurosurgery
Reg. Number:		Ext. Reference:	
NHS Number:		Date Received:	

Nature of Specimen: RIGHT PARIETAL LESION

Macro:

Irregular piece of firm grey tissue 1.5 x 0.9 x 0.8cm maximum dimension and a few tiny fragments.

Micro:

Sections show partly necrotic metastatic carcinoma set in heavily gliotic brain tissue. The appearance is more suggestive of squamous carcinoma than adenocarcinoma, but it is difficult to be certain.

Conclusion: Metastatic carcinoma.

TX2302 M8010/3

Reported by: **Date:**

see fig. 7

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NEUROPATHOLOGY

THE QUEEN ELIZABETH MEDICAL CENTRE, EDGBASTON, BIRMINGHAM B15 2TH
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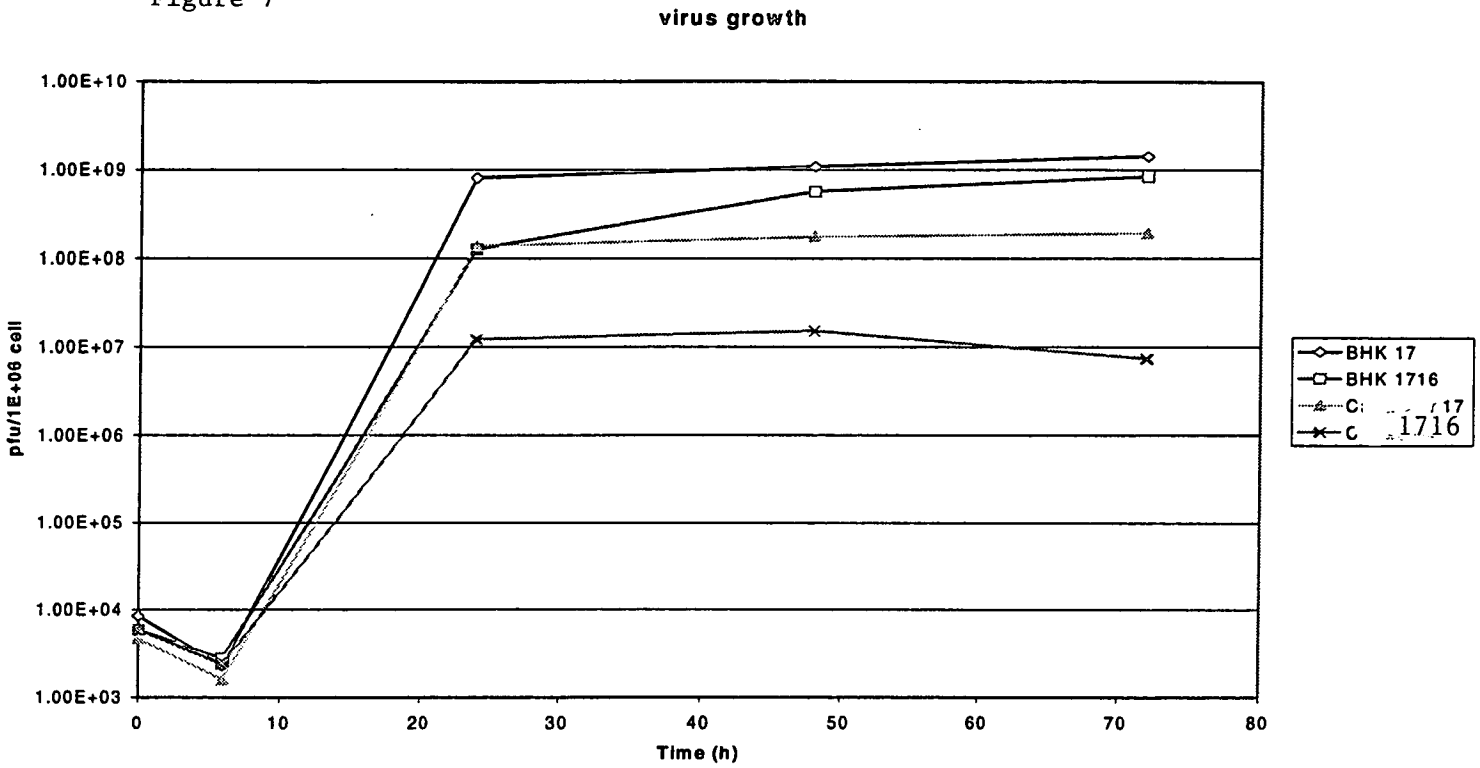
Figure 7


virus growth
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BHK 17
BHK 1716
1716

[redacted] Lab.No: [redacted]

Surname:
Forename: P
Date of Birth:
Sex:
Reg. Number:
NHS Number:

Consultant:
Hospital: **Queen Elizabeth Hospital, B'ham**
Ward: **Ward East Lower A (Neurosurg)**
Department: **Neurosurgery**
Ext. Reference:
Date Received:

Nature of Specimen: FRONTAL LOBE LESION

Macro:

A: Fragments of soft grey tissue together 1.2 x 1 x 0.5cm.
B: Frontal lobectomy specimen 7 x 5 x 3.5 maximum dimension. Cut surfaces show normal looking grey and white matter.

Micro:

A: Sections show malignant glioma of moderate to high cellular density composed of cells with markedly pleomorphic hyperchromatic nuclei and fibrillary cytoplasm. There are mitoses and apoptotic bodies, capillary endothelial proliferation and areas of necrosis. The appearance is that of glioblastoma. Stains for organisms are negative.

B: Cerebral cortex and subjacent white matter showing patchy infiltration by glioblastoma in several areas along the deep margin of the specimen.

Conclusion: Glioblastoma multiforme (astrocytoma grade 4).

TX2200 M9440/3

Reported by: **Date:**

see Fig. 8

NEUROPATHOLOGY

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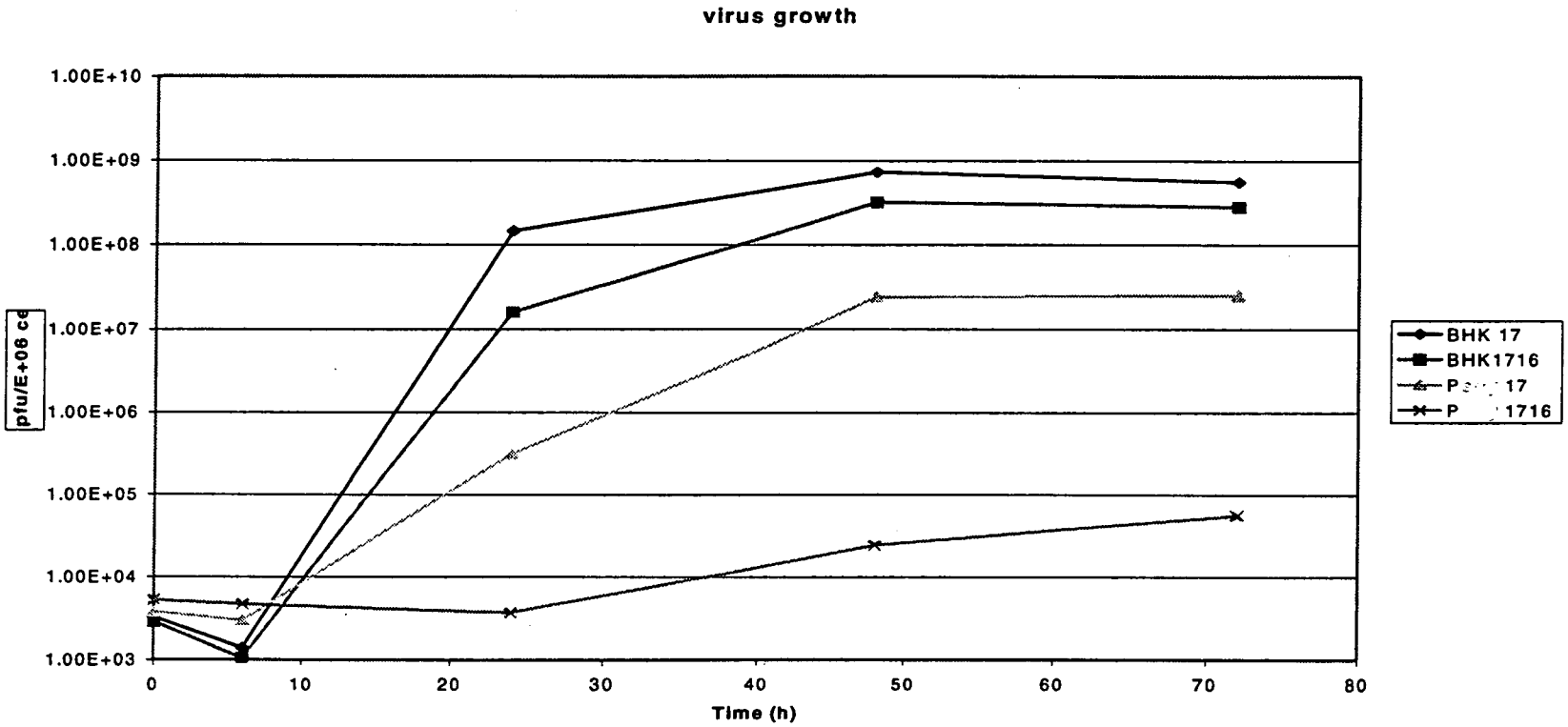
Figure 8


virus growth
1.00E+10
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Time (h)
BHK 17
BHK1716

NEUROPATHOLOGY DEPARTMENT

Lab.No.:

Surname:
Forename:
Date of Birth:
Sex: M
Reg. Number:
NHS Number:

Consultant:
Hospital: **Queen Elizabeth Hospital, B'ham**
Ward: **Ward East Lower B (Neurosurg)**
Department: **Neurosurgery**
Ext. Reference:
Date Received:

Nature of Specimen: RIGHT PARIETAL LESION

Macro:

Pieces of soft, grey tissue, some are small and two are up to 1cm.

Micro:

Section shows a cellular tumour composed of small, anaplastic glial cells with mitotic activity. There is geographical and serpiginous necrosis, and abundant microvascular hyperplasia is present.

There is also a tangle of large, atypical vessels reminiscent of an A-VM.

Diagnosis: Glioblastoma (astrocytoma grade 4).

TX2302 M9440/3

Reported by: **Date:**

See Fig. 9.

NEUROPATHOLOGY

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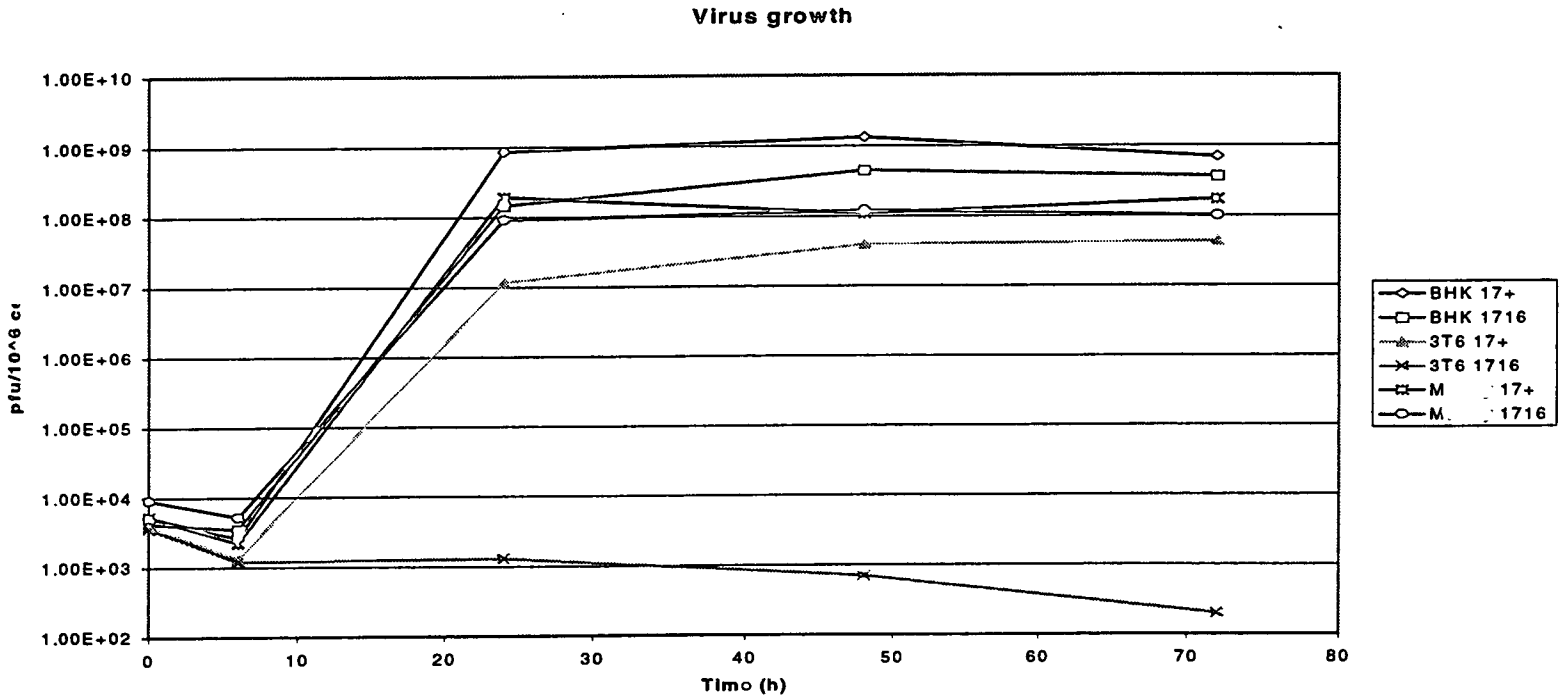
Figure 9.


Virus growth
1.00E+10
1.00E+09
1.00E+08
1.00E+07
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1.00E+05
1.00E+04
1.00E+03
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80
Time (h)
BHK 17+
BHK 1716
3T6 17+
3T6 1716
M 17+
M 1716

NEUROPATHOLOGY DEPARTMENT

Lab.No.:

Surname:
Forename:
Date of Birth: P1
Sex:
Reg. Number:
NHS Number:

Consultant:
Hospital: Queen Elizabeth H spital, B'ham
Ward: NCCU (Neuro Critical Care)
Department: Neurosurgery
Ext. Reference:
Date Received:

Nature of Specimen: SPENOIDAL LESION

Macro:

A - Irregular yellow tissue 0.6cm.
B - Pieces of irregular yellow and brown tissue 2cm.

Micro:

A. Section shows fragment of actively inflamed granulation tissue.

B. Section shows densely gliotic brain attached to actively inflamed collagen and granulation tissue. No organisms are seen on special stains but the appearances indicate infection. No definite evidence of neoplasia is seen.

TX2500 M4300

Reported by: **Date:**

see Fig. 10a

NEUROPATHOLOGY

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THE QUEEN ELIZABETH MEDICAL CENTRE, EDGBASTON, BIRMINGHAM B15 2TH
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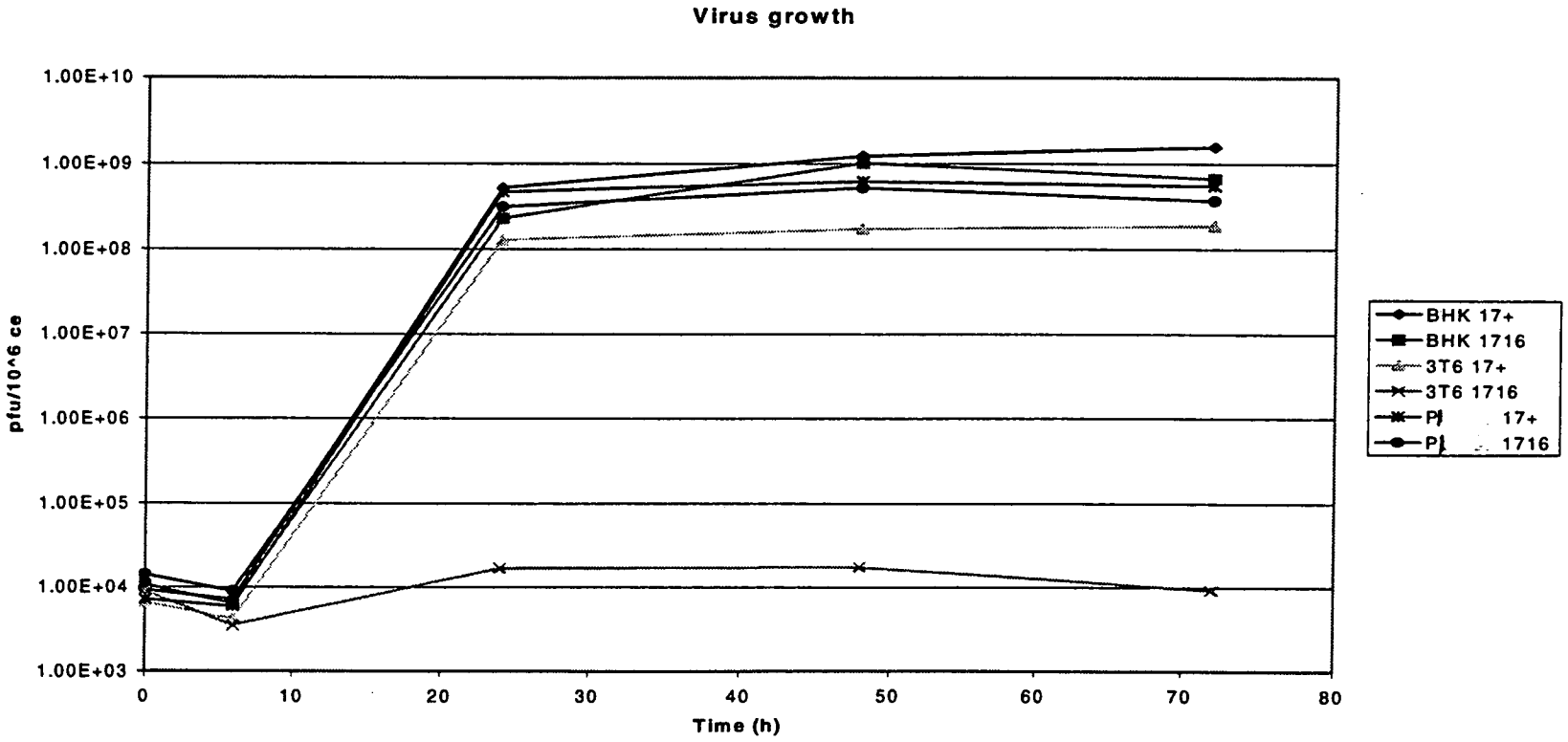
Figure 10a


Virus growth
1.00E+10
1.00E+09
1.00E+08
1.00E+07
1.00E+06
1.00E+05
1.00E+04
1.00E+03
pfu/10^6 ce
0
10
20
30
40
50
60
70
80
Time (h)
BHK 17+
BHK 1716
3T6 17+
3T6 1716
Pf 17+
Pf 1716

[redacted] Lab.No.:

Surname:
Forename:
Date of Birth:
Sex:
Reg. Number:
NHS Number:

G

Consultant:
Hospital: **Queen Elizabeth Hospital, B'ham**
Ward: **Ward East Lower B (Neurosurg)**
Department: **Neurosurgery**
Ext. Reference:
Date Received:

NEUROPATHOLOGY

Nature of Specimen: RIGHT OCCIPITAL LESION

Macro:

Nodule of firm, pale tissue, 1.5cm in diameter, slightly ragged external surface. Cut surfaces show patchy areas of necrosis.

Micro:

Sections show a mass of confluent necrotizing granulomatous inflammation with a thin rim of gliotic brain tissue in places. The granulomas contain masses of epithelioid cells and lymphocytes with well developed Langhans giant cells and large irregular areas of necrosis. Stains for bacterial and fungal organisms, including Ziehl-Neelsen stain for acid fast bacilli, are negative.

Comment:

In spite of the negative staining, this is almost certainly an infective process with tuberculosis by far the most likely organism. Other organisms such as yeasts and other fungi, spirochaetal infections etc cannot be excluded but are much less likely.

C nclusion:

Necrotising granulomatous inflammatory process, most likely tuberculosis. Other causes cannot be excluded.

TX2402 M44000

Reported by: **Date:**

See Fig. 10b

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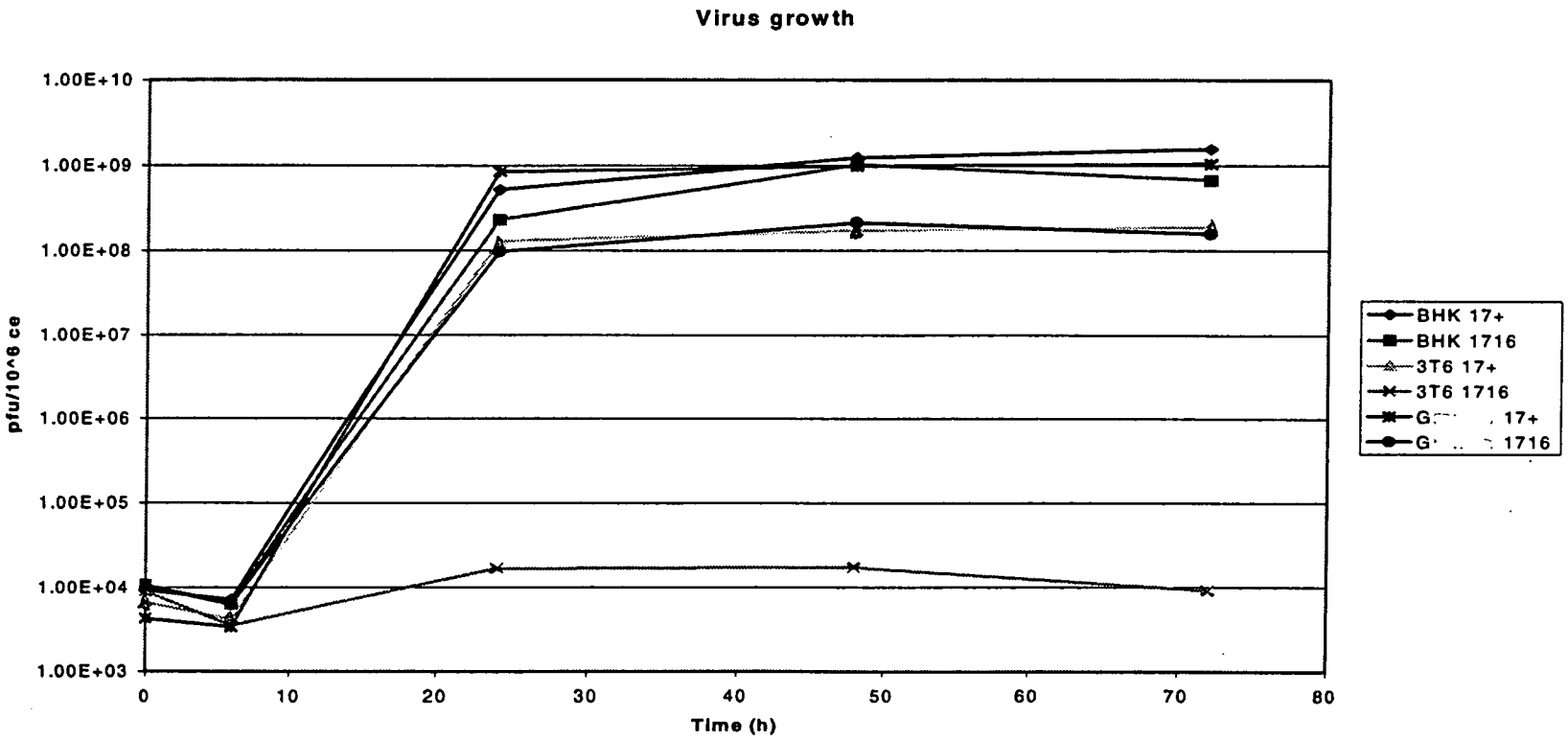
Figure 10b


Virus growth
1.00E+10
1.00E+09
1.00E+08
1.00E+07
1.00E+06
1.00E+05
1.00E+04
1.00E+03
pfu/10^6 ce
0
10
20
30
40
50
60
70
80
Time (h)
BHK 17+
BHK 1716
3T6 17+
3T6 1716

NEUROPATHOLOGY REPORT FORM

Lab.No.:

Surname:
Forename:
Date of Birth:
Sex:
Reg. Number:
NHS Number:

K1

Consultant:
Hospital: **Queen Elizabeth Hospital, B'ham**
Ward: **Ward East Lower B (Neurosurg)**
Department: **Neurosurgery**
Ext. Reference:
Date Received:

Nature of Specimen: LEFT PARIETAL LESION

Macro:

Irregular piece of soft, grey tissue 2 x 1.5 x 0.9cm maximum dimensions.

Micro:

Gliotic brain tissue containing areas of extensively necrotic metastatic adenocarcinoma, whose appearance is consistent with large bowel origin.

+

TX2303 M8140/6

Reported by: **Date:**

See Fig. 10

NEUROPATHOLOGY

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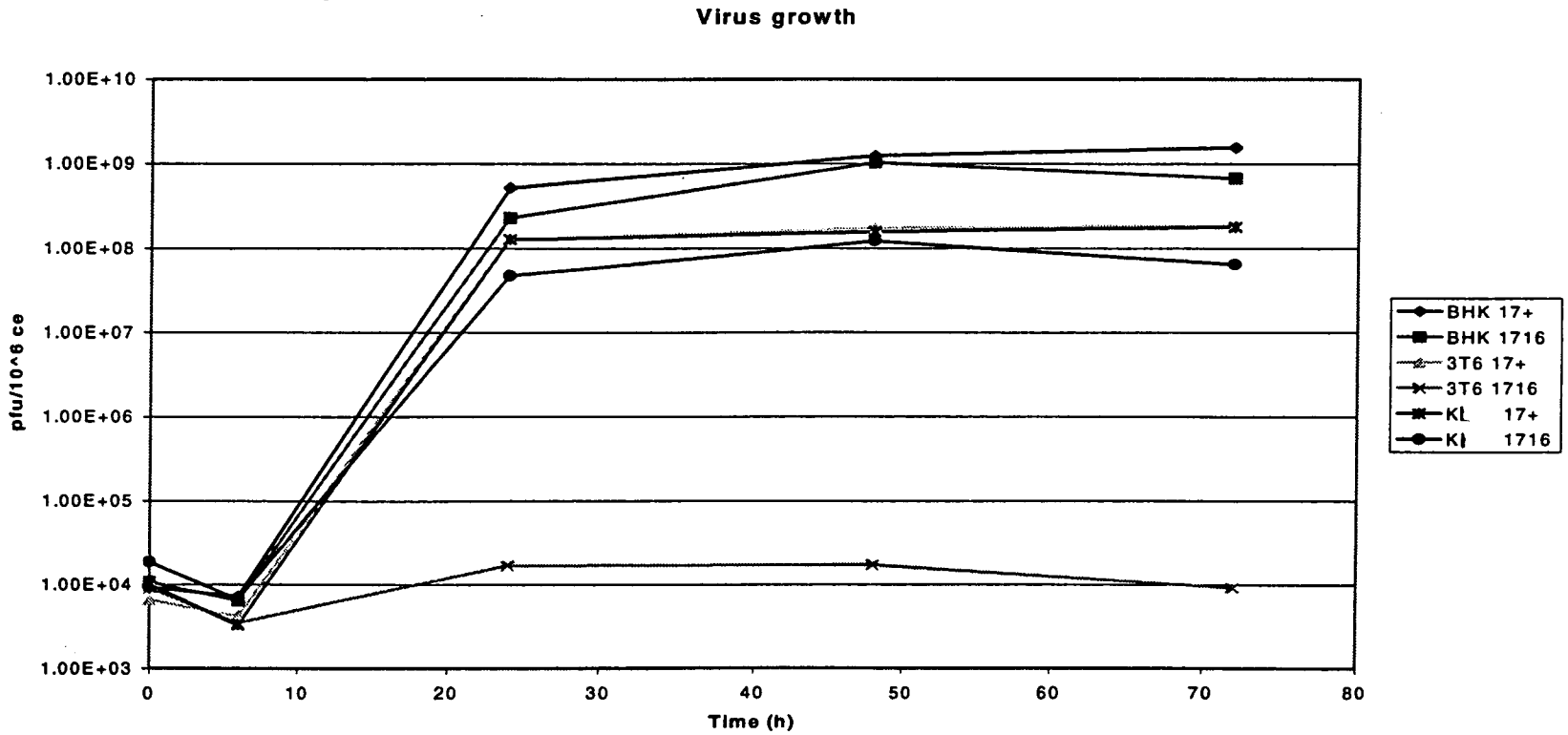
Figure 10c


Virus growth
1.00E+10
1.00E+09
1.00E+08
1.00E+07
1.00E+06
1.00E+05
1.00E+04
1.00E+03
pfu/10^6 ce
0
10
20
30
40
50
60
70
80
Time (h)
BHK 17+
BHK 1716
3T6 17+
3T6 1716
KL 17+
KL 1716